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# Mitochondrial dysfunction in neurological disorders with epileptic phenotypes

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**Abstract** A broad variety of mutations of the mitochondrial DNA or nuclear genes that lead to the impairment of mitochondrial respiratory chain or mitochondrial ATP synthesis have been associated with epileptic phenotypes. Additionally, evidence for an impaired mitochondrial function in seizure focus of patients with temporal lobe epilepsy and Ammon's horn sclerosis, as well as, animal models of temporal lobe epilepsy has been accumulated. This implies a direct pathogenic role of mitochondrial dysfunction in the process of epileptogenesis and seizure generation in certain forms of epilepsy.

**Keywords** Epilepsy · Mitochondrial DNA mutations · POLG · Mitochondria

## Introduction

The hallmark of epilepsy is recurrent epileptic seizures that, on a cellular level, consist of synchronized discharges of large groups of neurons which interrupt normal brain function. Epilepsy is the most common neurological disorder, affecting about 0.5–0.7% of the population worldwide. Recurrent seizures can occur as results of a broad variety of pathological alterations in the brain, like epileptogenic focal lesions (e.g. a brain tumour) or mutations in ion channel proteins. Apart from these primary causes, it is a well known fact that epileptic seizures can be presenting signs of mitochondrial dysfunction in the central nervous system. Thus, generalized seizures have been observed in several forms of myoclonus epilepsy associated with mutations in the mitochondrial DNA polymerase γ (*POLG*) (Naviaux and Nguyen 2004; Zsurka et al. 2008), mitochondrial $tRNA^{Lys}$ (*MT-TK*) (Shoffner et al. 1990; Zeviani et al. 1993) and $tRNA^{Phe}$ (*MT-TF*) (Zsurka et al. 2010) genes. Partial seizures are frequently noticed in mitochondrial encephalopathies, including the MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome, associated with mutations in the mitochondrial $tRNA^{Leu}$ gene (*MT-TL1*) (Goto et al. 1990, 1991). More recently, evidence for a more general involvement of mitochondria also in sporadic forms of epilepsy has been accumulated (Kann et al. 2005; Kunz et al. 2000; Kunz 2002). This might be related to the fact that mitochondria are intimately involved in pathways leading to neuronal cell death (Krajewski et al. 1999; Blümcke et al. 1999) seen in experimental and human epilepsy. On the other hand, more recent data substantiate the evidence, that mitochondrial dysfunction might play a direct pathogenic role in the process of epileptogenesis and seizure generation in certain types of epilepsy, such as temporal lobe epilepsy with Ammon's horn sclerosis, a therapy resistant form of epilepsy.

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## Mitochondrial dysfunction is associated with maternally inherited forms of epilepsy

An overview of the most common mitochondrial disorders presenting with an epileptic phenotype caused by mitochondrial DNA mutations is given in Table 1. A well known mitochondrial disorder with an epileptic phenotype, which is linked to point mutations in the mitochondrial DNA, is the MERRF (myoclonus epilepsy with 'ragged red

fibers') syndrome. This disease has been initially associated with mutations in the mitochondrial $tRNA^{Lys}$ (Shoffner et al. 1990; Zeviani et al. 1993). More recently, also several $tRNA^{Phe}$ mutations have been found to cause epileptic phenotypes (Hanna et al. 1998; Mancuso et al. 2004; Zsurka et al. 2010). As summarized in Table 1, a large list of mitochondrial DNA mutations has been detected in patients with epilepsy. The majority of these mutations are located in mitochondrial tRNA genes, and affect the protein biosynthesis of the mitochondrial-encoded subunits of NADH:CoQ oxidoreductase (complex I), of $CoQH_2$:cytochrome c oxidoreductase (complex III), of cytochrome c oxidase (complex IV), and $F_0F_1$-ATPase (complex V).

Quite rarely, also mutations in polypeptide-coding mitochondrial genes have been reported in patients with epilepsy—in the ATPase 6 gene, in the COI, COIII genes, in the cyt *b* gene, and in the ND1, ND2, ND3, ND5, ND6 genes (Table 1). The large variation in the clinical phenotype, even for a given mutation, is a well known feature of mitochondrial diseases. It is very common for these diseases, frequently associated with epilepsy, that the CNS, including the cortex, is significantly affected.

**Table 1** Epilepsy phenotypes in patients with mitochondrial DNA mutation related mitochondrial disorders

| General phenotype | Mitochondrial gene | Gene product | Mutations | References |
|---|---|---|---|---|
| MELAS | *MT-TL1* | $tRNA^{Leu(UUR)}$ | m.3243A>G, m.3271T>C, m.3252A>G, m.3256C>T, m.3260A>G, m.3291T>C | Goto et al. 1990, 1991, 1994, Morten et al. 1993, Nishino et al. 1996, Sato et al. 1994 |
| | *MT-TF* | $tRNA^{Phe}$ | m.583G>A | Hanna et al. 1998 |
| | *MT-TV* | $tRNA^{Val}$ | m.1642G>A | Taylor et al. 1996 |
| | *MT-TQ* | $tRNA^{Gln}$ | m.4332G>A | Bataillard et al. 2001 |
| | *MT-TC* | $tRNA^{Cys}$ | m.5814A>G | Manfredi et al. 1996 |
| | *MT-TK* | $tRNA^{Lys}$ | m.8296A>G, m.8316T>C, m.8356T>C | Sakuta and Nonaka 1989, Campos et al. 2000, Zeviani et al. 1993 |
| | *MT-CO3* | COX III | m.9957T>C | Manfredi et al. 1995 |
| | *MT-ND5* | ND5 | m.13513G>A | Santorelli et al. 1997 |
| | *MT-ND6* | ND6 | m.14453G>A | Ravn et al. 2001 |
| | *MT-CYB* | Cyt b | del 14787-90 | De Coo et al. 1999 |
| MERRF | *MT-TK* | $tRNA^{Lys}$ | m.8344A>G, m.8356T>C | Shoffner et al. 1990, Zeviani et al. 1993 |
| | *MT-TF* | $tRNA^{Phe}$ | m.611G>A, m.616T>C, m.616T>G | Mancuso et al. 2004, Zsurka et al. 2010 |
| Atypical MERRF | *MT-TL1* | $tRNA^{Leu(UUR)}$ | m.3255G>A | Nishigaki et al. 2003 |
| | *MT-TS1* | $tRNA^{Ser(UCN)}$ | 7472 Ins C | Pulkes et al. 2005 |
| | *MT-TD* | $tRNA^{Asp}$ | m.7543A>G | Shtilbans et al. 1999 |
| | *MT-TK* | $tRNA^{Lys}$ | m.8342G>A | Tiranti et al. 1999 |
| | *MT-TH* | $tRNA^{His}$ | m.12147G>A | Taylor et al. 2004 |
| | *MT-ND3* | ND3 | m.10191T>C | Taylor et al. 2001 |
| | *MT-ND5* | ND5 | m.13042G>A | Naini et al. 2005 |
| Seizures, PEO, diabetes, and deafness | *MT-TL1* | $tRNA^{Leu(UUR)}$ | m.3256A>G | Moraes et al. 1993 |
| Cardiomyopathy, deafness, and seizures | *MT-TI* | $tRNA^{Ile}$ | m.4269A>G, m.4320C>T | Taniike et al. 1992, Santorelli et al. 1995 |
| ME with recurrent episodes of epilepsia partialis continua | *MT-TS2* | $tRNA^{Ser(UCN)}$ | m.7512T>C | Jaksch et al. 1998 |
| | *MT-CO1* | COX I | m.6489C>A | Varlamov et al. 2002 |
| Leigh syndrome | *MT-ATP6* | ATP6 | m.8993T>G, m.8993T>C | Canafoglia et al. 2001, De Vries et al. 1993 |
| | *MT-TK* | $tRNA^{Lys}$ | m.8363G>A | Shtilbans et al. 2000 |
| LHON | *MT-ND1* | ND1 | m.3460G>A | Brown et al. 2001 |
| | *MT-ND2* | ND2 | m.4640G>A | Brown et al. 2001 |

ME, mitochondrial encephalopathy; MERRF, myoclonus epilepsy with 'ragged red fibers'; MELAS, myopathy, encephalopathy with lactic acidosis and stroke-like episodes; PEO, progressive external ophthalmoplegia; LHON, Leber's hereditary optical neuropathy.

Imaging techniques have confirmed that grey matter involvement is an early feature of MERRF and MELAS, however, also white matter changes have been seen at later stages of the disease, but usually not in isolation (Cock and Schapira 1999). A mosaic distribution of mutant mtDNA has been documented for MERRF and MELAS mutations leading to different proportions of wild-type and mutant mtDNA (so called heteroplasmy) in different tissues and even in individual neurons. Since mtDNA mutations are known to have a substantial influence on oxidative phosphorylation only when they accumulate beyond a certain threshold level (Schröder et al. 2000), a largely varying extent of biochemical defects is possible in different tissues. This phenomenon can at least in part explain the large phenotypic variation of these diseases.

## Mitochondrial dysfunction is associated with autosomally inherited forms of epilepsy

Epileptic seizures have also been observed frequently in mitochondrial encephalopathies related to mutations in nuclear genes. An overview of the most common nuclear encoded mitochondrial disorders presenting with an epileptic phenotype is given in Table 2. Thus, mutations in mitochondrial DNA polymerase γ (*POLG*) have been associated not only with autosomal dominant (adPEO) (Suomalainen et al. 1997; Van Goethem et al. 2001) and recessive (Van Goethem et al. 2001) forms of progressive external ophthalmoplegia (PEO) and a certain form of ataxia (Winterthun et al. 2005), but also quite frequently with a severe epilepsy of childhood, called Alpers-Huttenlocher syndrome (Naviaux and Nguyen 2004; Zsurka et al. 2008). In addition to severe epilepsy, frequently presenting as epilepsia partialis continua, all affected Alpers-Huttenlocher patients suffer from various manifestations of a severe systemic mitochondrial disease—mainly brain and liver being affected. The major biochemical defect is a severe depletion of mtDNA, markedly pronounced in liver and explaining the severe toxicity of valproic acid in these patients (Zsurka et al. 2008). A further mitochondrial disease presenting frequently with epilepsy is the Leigh syndrome. This disease is very heterogeneous, both biochemically and genetically, involving mutations both in nuclear and mitochondrial genes (cf. Tables 1 and 2).

## Mitochondrial dysfunction in human and experimental temporal lobe epilepsy (TLE)

The majority of epilepsy patients suffer from focal epilepsies that frequently develop subsequently to brain trauma, complicated febrile convulsions, status epilepticus, ischemic lesions and brain tumours. One of the most frequent and devastating forms of epilepsy involves the development of an epileptic focus in temporal lobe structures and is usually associated with hippocampal sclerosis (HS). In addition to the neuropathological abnormalities observed in hippocampal sclerosis also biochemical defects of mitochondria have been reported in the areas of epileptogenesis. Thus, a severe impairment of respiratory chain complex I activity was observed in CA3 hippocampal subfields from patients with HS and in the parahippocampal gyrus of patients with parahippocampal lesions (Kunz et al. 2000). These data were supported by a study in which applying interictal [18 F]fluorodeoxyglucose positron emis-

**Table 2** Epilepsy phenotypes in patients with nuclear gene-related mitochondrial disorders

| Type of defect | Biochemical defect | Clinical phenotype | Defective gene |
|---|---|---|---|
| Defects of intergenomic communication | mtDNA depletion | Alpers syndrome | *POLG* |
| | mtDNA depletion | Infantile encephalopathy and hepatopathy | *DGUOK* |
| | mtDNA depletion | Infantile encephalomyopathy | *SUCLG1* |
| | multiple mtDNA deletions | MNIGIE | *TYMP* |
| Mutations in genes encoding structural subunits of respiratory chain | complex I deficiency | Leigh syndrome or encephalomyopathy | *NDUFS1*, *NDUFS2*, *NDUFS3*, *NDUFS4*, *NDUFS6*, *NDUFS7*, *NDUFS8*, *NDUFV1*, *NDUFV2* |
| | complex II deficiency | Leigh syndrome | *SDHA* |
| Mutations in genes encoding assembly factor of respiratory chain enzymes | complex I deficiency | Encephalopathy | *NDUFA12* |
| | complex III deficiency | Encephalopathy, tubulopathy and hepatopathy | *BCS1L* |
| | complex IV deficiency | Leigh syndrome | *SURF1* |
| | complex IV deficiency | Infantile cardioencephalo-pathy | *SCO2* |
| | complex IV deficiency | Infantile encephalo-pathy | *SCO1*, *COX10* |

Table modified according to M. Hirano et al. (2008). Please note, that Alpers syndrome is the most frequent phenotype.

sion tomography the degree of hippocampal glucose hypometabolism in HS patients determined *in vivo* was strongly correlated to the respiratory activity of the CA3 subfield determined *in vitro* (Vielhaber et al. 2003a). Applying high resolution NMR spectroscopy, low N-acetyl aspartate (NAA) concentrations were found to be restricted to the CA3 subfield. In other subfields, like CA1 experiencing an even more intense cell loss, normal levels were observed. Furthermore, a considerable increase of lactate and succinate was also observed in the CA3 subfield, further emphasizing the region-specificity of mitochondrial impairments (Vielhaber et al. 2008). An about two-fold decrease in the copy number of mitochondrial DNA and of aconitase activity was observed in the hippocampal CA3 subfield of patients with HS, providing one molecular cause for the observed decrease in activity of the mitochondrial respiratory chain (Baron et al. 2007). Additionally, abundant deletions of mitochondrial DNA showing an abnormal deletional spectrum were observed in hippocampal tissue of epilepsy patients with HS (Guo et al. 2010). And finally, pronounced drops of NAD(P)H fluorescence transients compatible with an impairment of mitochondrial function were observed in human tissue from patients with TLE (Kann et al. 2005). These finding were interpreted in support of the hypothesis that the hypometabolism in the epileptic focus is more a reflection of dysfunction in cellular energy metabolism rather than neuronal cell loss (see also O'Brien et al. 1997).

Taken together, these findings strengthen the viewpoint of a putative underlying metabolic dysfunction as an important pathophysiological mechanism in human temporal lobe epilepsy with HS. As a potential molecular cause of the detected local impairment of the mitochondrial respiratory chain, a decrease of the mtDNA copy number and/or mtDNA deletions can be delineated, very similar to Alpers-Huttenlocher syndrome. This similarity supports the viewpoint that the mitochondrial dysfunction in the seizure focus of HS patients is not only relevant for the progressive neuronal cell death, but directly involved in seizure generation.

In the recent literature there are also accumulating hints for the contribution of oxygen radicals in the process of epileptogenesis and in chronic experimental epilepsy showing progressive neuronal cell death. There is evidence for the increased generation of oxygen radicals in status epilepticus induced by kainate or pilocarpine (Frantseva et al. 2000; Liang et al. 2000) and in the low-magnesium model of epileptoform activity (Kann et al. 2003; Kovács et al. 2002; Schuchmann et al. 2002). These oxygen radicals are primarily generated by the mitochondrial respiratory chain (Kudin et al. 2008; Malinska et al. 2010). During inhibition of the respiratory chain, considerable amounts of superoxide are produced, which can overload the endogenous protective enzymes (glutathione peroxidase, superoxide dismutase, catalase) resulting in an oxidative damage of proteins, phospholipids and of mitochondrial DNA. The other way around, oxygen radicals themselves can inhibit the respiratory chain (Kudin et al. 2004), which creates a vicious cycle. In the process of epileptogenesis an initial oxidative stress linked with status epilepticus causes, very likely by this mechanism, progressive impairment of respiratory chain complexes in the vulnerable CA1 and CA3 hippocampal subfields of pilocarpine-treated chronic epileptic rats (Kudin et al. 2002).

## Hyperexcitability caused by mitochondrial dysfunction

The potential direct links between impairment of mitochondrial function and the increased neuronal excitability causing epilepsy are decreased intracellular ATP levels and alterations of neuronal calcium homeostasis.

The importance of high neuronal ATP levels is supported by the findings that epileptic seizures are observed in Leigh syndrome patients harboring the mutations m.8993T>G and m.8993T>C in the *MT-ATP6* gene (De Vries et al. 1993; Canafoglia et al. 2001) affecting activity of mitochondrial $H^+$-ATPase. Under the conditions of inhibition of $H^+$-ATPase, mitochondria have a high membrane potential enabling effective mitochondrial ion transport. Accordingly, in cybrids with the m.8993T>G mutation normal mitochondrial calcium handling was observed, while cellular ATP levels were markedly decreased (Brini et al. 1999).

It is further well established that neuronal mitochondria are important for intracellular $Ca^{2+}$ sequestration (Tang and Zucker 1997). Due to this feature, mitochondria also can modulate neuronal excitability and synaptic transmission (Bindokas et al. 1998; Tang and Zucker 1997), which is altered in epilepsy. In agreement with this concept, impaired oxidative phosphorylation due to $Ca^{2+}$ cycling at the inner membrane of hippocampal mitochondria has been demonstrated in kainate-treated chronic epileptic rats (Kunz et al. 1999). Impaired cellular $Ca^{2+}$ homeostasis due to substantial alterations of mitochondrial $Ca^{2+}$ handling was the predominant feature of cybrid cells harbouring the mitochondrial *MT-TK* mutation m.8356T>C being associated with MERRF (Brini et al. 1999).

The impact of mitochondrial dysfunction on neuronal hyperexcitability is less clear in temporal lobe epilepsy with hippocampal sclerosis. It has to be underlined that the mitochondrial pathology is a prominent feature of not only the CA3 pyramidal subfield (Baron et al. 2007; Kunz et al. 2000; Vielhaber et al. 2003b; Vielhaber et al. 2008) alone, but has been also detected in the hilar neurons of dentate gyrus (Blümcke et al. 1999), comprising mainly

mitochondria-rich inhibitory interneurons. These mitochondria-rich interneurons are parvalbumine-positive (Gulyás et al. 2006) and determinants of hippocampal theta rhythm and its coupling with gamma oscillations (Wulff et al. 2009). Therefore it is reasonable to speculate, that the compromised energy metabolism of this particular neuronal population might be responsible for the misbalance between neuronal excitation and inhibition characteristic for this form of epilepsy (cf. also Kudin et al. 2009).

Taken together, mitochondria are proposed to be of high relevance for seizure generation in certain forms of epilepsy. Therefore, they should be considered as promising targets for future therapeutic strategies in this frequent neurological disorder.

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